Induction of mucosal and systemic responses against human immunodeficiency virus type 1 glycoprotein 120 in mice after oral immunization with a single dose of a Salmonella-HIV vector.

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Previous studies from our group showed that a Salmonella-HIV vector vaccine that expressed recombinant HIV-1 envelope protein gp120 stably in the vector cytoplasm elicited type 1 helper T cell (Th1) responses to gp120. Despite the promise of such vaccines, a major limitation in their use was that multiple immunizations were required to elicit even small responses. For this reason, we sought a modified vector configuration that would induce more potent gp120-specific T cell responses exhibiting a broader spectrum of effector functions after a single inoculation. In this article we describe the construction and immunogenicity of a Salmonella-HIV vector that displays a truncated derivative of HIV-1(IIIB) envelope in the periplasm of the vector. A single oral dose of this Salmonella vector, called H683(pW58-asd+), generated a gp120-specific proliferation response in the spleen 14 days after immunization. In agreement with our previous findings, the gp120-specific splenic CD4+ T cells elicited by H683(pW58-asd+) displayed a Th1 phenotype; however, gp120-specific splenic CD4+ Th2 cells were also evident. In addition, this strain induced strong gp120-specific IgA antibody-secreting cell (ASC) responses in the intestinal lamina propria and mesenteric lymph nodes. As many as 2% of the total lamina propria and mesenteric lymph node IgA ASCs were found to be specific for gp120 28 days after a single oral dose of H683(pW57-asd+). Because the proliferative response following a single dose of H683(pW58-asd+) was comparable to that seen previously after three doses of an analogous construct expressing recombinant gp120 in the cytoplasm, these observations suggest that Salmonella-vectored secreted HIV-1 antigens elicit higher T cell responses than their cytoplasmically bound analogs.

1: J Virol. 1994 Mar;68(3):1624-32. Related Articles, Links

Mucosal model of genital immunization in male rhesus macaques with a recombinant simian immunodeficiency virus p27 antigen.

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Human immunodeficiency virus (HIV) can be transmitted through infected seminal fluid or vaginal or rectal secretions during heterosexual or homosexual intercourse. To prevent mucosal transmission and spread to the regional lymph nodes, an effective vaccine may need to stimulate immune responses at the genitourinary mucosa. In this study, we have developed a mucosal model of genital immunization in male rhesus macaques, by topical urethral immunization with recombinant simian immunodeficiency virus p27gag, expressed as a hybrid Ty virus-like particle (Ty-VLP) and covalently linked to cholera toxin B subunit. This treatment was augmented by oral immunization with the same vaccine but with added killed cholera vibrios. Polymeric secretory immunoglobulin A (sIgA) and IgG antibodies to p27 were induced in urethral secretions, urine, and seminal fluid. This raises the possibility that the antibodies may function as a primary mucosal defense barrier against SIV (HIV) infection. The regional lymph nodes which constitute the genital-associated lymphoid tissue contained p27-specific CD4+ proliferative and helper T cells for antibody synthesis by B cells, which may function as a secondary immune barrier to infection. Blood and splenic lymphocytes also showed p27-sensitized CD4+ T cells and B cells in addition to serum IgG and IgA p27-specific antibodies; this constitutes a third level of immunity against dissemination of the virus. A comparison of genito-oral with recto-oral and intramuscular routes of immunization suggests that only genito-oral immunization elicits specific sIgA and IgG antibodies in the urine, urethra, and seminal fluid. Both genito-oral and recto-oral immunizations induced T-cell and B-cell immune responses in regional lymph nodes, with preferential IgA antibody synthesis. The mucosal route of immunization may prevent not only virus transmission through the genital mucosa but also dissemination and latency of the virus in the draining lymph nodes.

Oral priming followed by parenteral immunization with HIV-immunosomes induce HIV-1-specific salivary and circulatory IgA in mice and rabbits.

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PMID: 1466960 [PubMed - indexed for MEDLINE]

1: AIDS. 1994 Jun;8(6):779-85.

Immune response following oral administration of cholera toxin B subunit to HIV-1-infected UK and Kenyan subjects.

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OBJECTIVE: To determine the effect of HIV-1 infection on immunoglobulin (Ig) G and IgA antibody response and circulating antibody forming cell response to oral immunization with the B subunit of cholera toxin. DESIGN: Healthy UK volunteers, and HIV-1-positive UK and Kenyan volunteers at different clinical stages of HIV-1 infection received two oral immunizations. CD4+ T cells, serum beta 2-microglobulin and neopterin were measured as surrogate markers of disease stage, and correlated with immunization response. METHODS: Serum antitoxin IgG and IgA measured by enzyme-linked immunosorbent assay and antitoxin IgG, IgA and IgM antibody-forming cells detected by enzyme-linked immunospot assay at different times after two oral immunizations. RESULTS: UK HIV-positive volunteers (mean CD4+ T cell count, 52 x 10(6)/l) responded poorly to primary and booster immunization. HIV-infected Kenyans (752 x 10(6)/l CD4+ T cells) had a significant primary and booster antibody response, whereas those with a mean CD4+ T cell count 186 x 10(6)/l had an insignificant primary, but significant booster response. Two oral immunizations induced antibody responses in HIV-positive Kenyan groups (who may have prior immunity from exposure to environmental bacterial toxins) of similar or greater magnitude to healthy UK volunteers. CONCLUSIONS: Mucosal immunization may recall immune memory and be of benefit in early and moderately advanced clinical HIV disease. The findings have important clinical implications in that mucosally targeted vaccines are potentially useful in this group of patients.

PMID: 8086136 [PubMed - indexed for MEDLINE]

1: Oral Dis. 1997 May;3 Suppl 1:S79-84. Related Articles, Links

Salivary and mucosal immune responses to HIV and its co-pathogens.

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The profound effects that HIV induces in systemic immunity have been well characterised, but the situation with regard to mucosal immune responses is less clear. Oral cavity fluids have been used as a marker of the mucosal immune system. Whole and parotid saliva IgA, IgA1 and IgA2 concentrations have been found to be lower in both HIV infection and AIDS subjects, whereas serum IgA and IgA subclasses are markedly raised, suggesting a dichotomy between systemic and secretory immunity. Salivary antibodies to HIV can be readily detected and secretory IgA antibody can be neutralising to some strains of HIV. HIV vaccines can also induce antibody responses in saliva, but vaccination routes other than parenteral immunisation are needed. Antibody responses to oral microbes have also been studied and it has been shown that IgA, IgA1 and IgA2 subclass antibody titres to Candida albicans and to Streptococcus mutans are increased in whole or parotid saliva from HIV patients, but reduced in AIDS patients, suggesting a compensatory response which is overcome with progressive immunodeficiency. The avidity of salivary IgA antibodies to Candida in HIV seems unimpaired, whereas relative avidities of serum antibodies in HIV patients with candidiasis are lowered. Non-specific factors which may inhibit Candida and other opportunist pathogens are also found in saliva. The candidacidal, myelomonocytic protein calprotectin is present in saliva at levels which are biologically active, although levels are lowered in HIV infection. Overall, HIV infection appears to be associated with disregulation of a number of immune factors at the mucosal surface, but the ability of patients with HIV infection to mount specific antibody secretory responses seems to be relatively intact until late in infection.

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